Differential Control of the Calcium-Dependent Transcription Factors NFAT and NFκB during T-Cell Activation

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We have developed mathematical models for the regulation of the Ca^{2+}-dependent transcription factors NFAT and NFκB that are involved in the activation of the immune and inflammatory responses in T lymphocytes. In resting cells, phosphorylation blocks the nuclear localization signals on NFAT, as does association of NFκB with the inhibitor IκB. Consequently both NFAT and NFκB are retained in the cytoplasm. T cell receptor stimulation initiates a cascade of reactions that cause an increase in intracellular Ca^{2+} concentration. Activated by the increase in Ca^{2+}, calcineurin dephosphorylates NFAT, while the kinase IKK phosphorylates IκB bound to NFκB initiating the polyubiquitination and subsequent degradation of the IκB. As a result, nuclear localization signals are exposed on both NFAT and NFκB allowing translocation of their free and transcriptionally active forms to the nucleus where they can promote gene transcription. Our models simulate 1) activation and deactivation over physiological Ca^{2+} concentrations; 2) differential response of NFAT and NFκB to the frequency of Ca^{2+} concentration oscillations as reported by Dolmetsch, Xu, and Lewis (1998); and 3) enhancement of the activity of NFAT by Ca^{2+} oscillations at low calcium concentrations. The model suggests the mechanism by which transcription factor residence time in the nucleus is controlled by calcium signaling. The model also suggests that IκB degradation is essential for efficient translocation of NFκB to the nucleus.